

Downstaging of hepatocellular carcinoma with radiofrequency ablation on the Hungarian liver transplantation waiting list – Early results and learned lessons

E. HARTMANN* ■ A. NÉMETH ■ GY. JUHAROSI ■ ZS. LÉNÁRD ■ P. Á. DEÁK ■ V. KOZMA ■ P. NAGY ■ ZS. GERLEI ■ I. FEHÉRVÁRI ■ B. NEMES ■ D. GÖRÖG ■ J. FAZAKAS ■ L. KÓBORI ■ A. DOROS

Semmelweis University, Clinic for Transplantation and Surgery

*Corresponding author: Dr. Hartmann Erika, Baross u. 23–25, H-1082 Budapest, Hungary

Phone: +36 20 8258573 • E-mail: hartmann.erika@gmail.com.

Abstract: Hepatocellular carcinoma, which has developed in liver cirrhosis is a disease where liver transplantation can provide a cure both for the tumour and the underlying liver damage. However, patients can only be transplanted when the tumour number and size do not exceed the Milan criteria. Tumour ablation methods – such as radiofrequency ablation – can provide a chance to make the patient eligible for transplantation. Among the 416 Hungarian liver transplanted patients there are 6 who had received different types of ablative therapy as bridging therapy in different institutions. On the basis of analysis of the patients' data we created a guideline for the treatment of cirrhotic patients with hepatocellular carcinoma with the aim of developing a uniform Hungarian approach.

Keywords: cirrhosis, hepatocellular carcinoma, liver transplantation, waiting list, tumour ablation therapy, radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC), is one of the most common cancers worldwide that usually develops in an already damaged, often cirrhotic liver. Among others, the aetiology of background liver disease is mainly cirrhosis caused by chronic hepatitis B or C viral infection (HBV/HCV). During treatment, not only HCC itself but also the background liver disease should be targeted. Liver transplantation (LT) guarantees the best long-term and disease-free survival because it removes the cirrhotic liver with the tumour. However, the shortage of organs only allows treating a small proportion of patients by LT [1, 2]. According to the Milan criteria for liver transplantation with HCC, a patient can only be transplanted if the nodule is not larger than 5 cm or, in cases of multiplex nodules, if there is a maximum of 3 nodules with the largest not exceeding 3 cm in diameter. Therefore disease progression produces a 25% dropout rate from the waiting lists [3].

Surgical and interventional treatments of HCC, known as downstaging, are widely accepted as bridging therapies to LT, in other words, as therapies with the ability to keep patients on the waiting list [4]. Among the several abla-

tive methods, radiofrequency ablation (RFA) appears to be one of the most efficient percutaneous technique for HCC ablation. Other methods, such as percutaneous ethanol infiltration (PEI) or transarterial chemoembolization (TACE), are used with less favourable results in terms of recurrence or tumour control [5, 6]. RFA seems to be the best technique thanks to its predictable area of induced necrosis and percentage of induced necrotic cells [7].

In these RFA procedures, an ablation electrode at the tip of a needle is placed percutaneously into the targeted tumour under imaging guidance. Radiofrequency electromagnetic waves are transmitted from a generator and converted to heat, thus inducing necrosis in the tissues around the electrode.

The Hungarian Liver Transplant Program started in 1995, and during these years 416 LTs have been performed [8]. RFA became available for downstaging in 2004, though with limited financial resources [9]. From 2004 until the end of 2008, several ablated patients underwent successful LT, allowing their data to be analyzed.

The aim of this report is to determine important factors, such as lesion number, size, histopathologic type, treat-

ment type and time interval between treatment and LT, based on explanted liver histology and to make important refinements of patient selection and treatment protocol.

Patients and Methods

Between 2004 and 2008 we had six liver transplanted patients (2 females, 4 males, with a mean age of 56 years) who were treated with RFA earlier. Five out of six patients had HCV infection related cirrhosis and one had ALD (alcoholic liver disease) related cirrhosis. None of the patients had hepatitis B in their medical history. All the patients with HCV infection underwent targeted antiviral therapy. There were three Child–Pugh Class A and three Child–Pugh Class B patients. In these six patients nine HCC nodules were identified with preoperative imaging techniques, such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). Eight lesions were identifiable with US, eight with CT and six with MRI. Pre-treatment fine needle aspiration biopsy (FNAB) was performed in all patients but not in all lesions.

The bridging therapies and their follow-up imaging tests were carried out in different medical centres. RFA was guided by US (Fig. 1) in four patients, and with CT (Fig. 2) in two patients. MRI guidance was not used, since it is unavailable in Hungary. In three lesions of two patients single 16-gauge open-perfused needle electrodes (Berchtold Medizinelektronik) were applied. One patient with one lesion was treated with the MIRAS device (Invatec) and three patients with five lesions (one, one and three, respectively) were ablated with the RITA Starburst system (Angiodynamics). One patient required general anaesthesia, four patients were ablated under conscious sedation, and one treatment could be performed under local anaesthesia. Two patients received additional PEI and one patient received chemoperfusion.

At follow-ups, multiphase contrast-enhanced CT scans or MRI were performed. The mean time between initial treatment and transplantation was 8.6 months (2–35 months) while the mean time between the last treatment to transplantation was 10.2 months (2–35 months).

All the transplantations were performed from cadaveric donors; no living donation or split transplantation were needed.

The explanted livers were processed and analyzed to assess the degree of tumour necrosis and the signs of vascular invasion (Fig. 3).

The mean post-transplant follow-up was 23.3 months (3–46 months) (Table I).

Results

During the post-ablation follow-up period 4 lesions showed complete necrosis whereas 5 lesions showed only partial response on contrast-enhanced CT or MRI images. Histological examination of the explanted livers revealed more than 14 countable lesions and in one patient

(Nr. 2) several additional small HCC nodules were found. In this patient microscopic vascular invasion was also diagnosed. The lesions were trabecular, except for one that showed diffuse morphology. All of the lesions were grade 2 or 3. Only one of the 9 lesions was completely necrotized at the time of transplantation, while in 7 lesions only partial necrosis could be found. One treated nodule showed no necrosis at all.

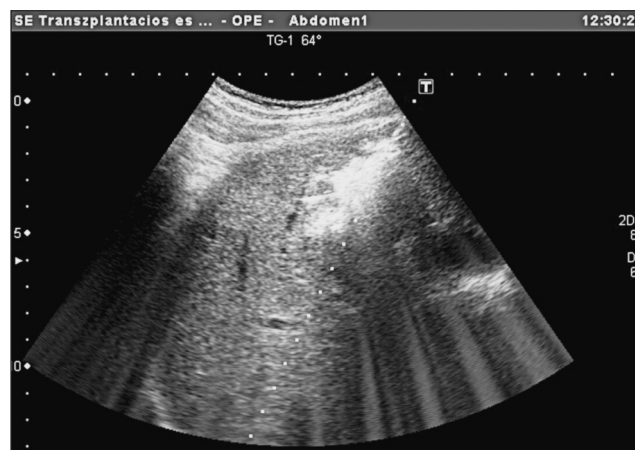


Fig. 1. ■ Ultrasound-guided RFA ablation

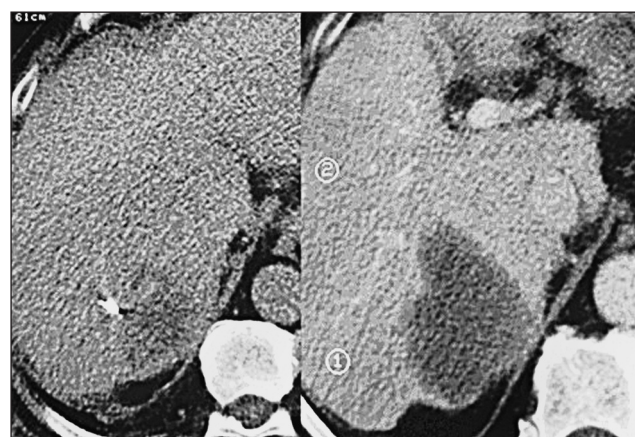


Fig. 2. ■ CT-guided RFA ablation. Non contrast CT shows the tip of the needle at the border of the tumour. Follow-up contrast enhanced CT image shows complete necrosis



Fig. 3. ■ Necrosis in the tumour in the explanted liver

Table I. ■ Relevant data of six patients who underwent ablative downstaging before orthotopic liver transplantation

Pt. Nr	Child-Pugh score	HCV	HBV	DT first treatment to LT	DT last treatment to LT	Mode and Nr. of treatment	Nr. of treated HCC	Nr. of HCC in the explanted liver	Degree of necrosis on imaging	Degree of necrosis on histology	PVT	Total size of HCC on imaging (mm)	Immuno-suppression	Follow up (months)	Recurrent HCC	Exit
1	B	yes	no	6.5	3.7	2 × RFA	1	2	partial	partial	no	43	FK + steroid + Eve	2.7	no	no
2	A	yes	no	35.5	35.5	1 × RFA	1	multilobar	complete, but recurrence	minimal	yes	26	FK + steroid + MMF	10.2	no	no
3	A	yes	no	2	2	1 × RFA	1	1 + 1 DN	one partial (80%)	66%	no	32	CyA + steroid + MMF	26.8	no	no
4	B	yes	no	7.4	2.4	1 × RFA + 2 × PEI	1	2	one partial, (90%)	60%	no	51	FK + steroid + MMF	41.6	yes	no
5	A	yes	no	3.5	1.5	1 × RFA + 4 × ChP	2	2	complete	partial	no	22	FK + steroid + MMF	46.5	no	no
6	B	no	no	6.5	6.3	1 × RFA + 1 × PEI	3	2 + 4 DN	two partial, one complete	50%/100%, no necrosis in 1 DN	no	75	FK + steroid + MMF, later FK + Eve	12.1	yes	no
				10.2	8.6	14.0	9	> 14			1	41.5		23.3	2	0

(Abbreviations: HCV/HBV – hepatitis C/B viral infection; LT – liver transplantation; DT – time interval between treatments and LT; RFA – radiofrequency ablation; PEI – percutaneous ethanol infiltration; ChP – chemoperfusion; DN – high grade dysplastic nodule; PVT – portal vein thrombosis/invasion; FK – FK-506; MMF – mycophenolate mofetil; Eve – everolimus)

The time interval between the first and the last treatment and the liver transplantation was 8.6 and 10.2 months, respectively, but patient Nr. 2 had a time interval of 35.5 months, during which period the above-mentioned multilobar recurrences were able to develop.

All the liver transplantations were successful, without evidence of vascular and/or biliary complications. One reoperation was performed due to postoperative bleeding, and one patient developed small bowel perforation 3 weeks after transplantation, necessitating surgical intervention.

For the time being, four out of six patients are fine with acceptable liver function tests and no signs of recurrence or metastasis. One patient (Nr. 4) with a larger HCC (initial size: 51 mm) recently developed extrahepatic (left pleural) HCC recurrence and the second patient (Nr. 6) (initial size: 75 mm) retroperitoneal HCC recurrence after 41.6 and 12.1 months, respectively. These two patients waited for transplantation for more than 6 months (7.4 and 6.5 months). The third patient (Nr. 1), with a longer waiting time, has the shortest follow-up. There was no obvious relationship between recurrence and immunosuppression, or tumour characteristics in this small group of patients.

Discussion

Small and medium sized HCC accompanied with end-stage liver cirrhosis can be most effectively treated with liver transplantation (LT). Theoretically, transplantation

might simultaneously cure the tumour and the underlying cirrhosis. Candidates who are eligible for LT should have one HCC smaller than 5 cm or the maximum of three nodules that are smaller than 3 cm [10] and can achieve a 70% survival rate at 5 years, with a recurrence rate lower than 15%. Tumour progression on the waiting list is a crucial point worldwide, because the benefit of transplantation could only be obtained if the waiting time does not exceed 6 months [11]. The shortage of donors clearly limits the potential benefits of cadaveric liver transplantation [1]. Various methods have been available to reduce the dropout-rate from the waiting list by applying adjuvant therapies for HCC. Liver resection can be performed in cases with preserved liver function, followed by salvage liver transplantation [12, 13]. There are reports demonstrating the effectiveness of chemoembolization [14, 15]. Local ablation therapies for HCC, such as PEI and RFA, can be performed safely and effectively in compensated cirrhosis [16]. Furthermore, combinations of therapies could also be an option in selected cases [17].

In a study by Yamashiki et al., 288 patients with HCC on a virtual waiting list were treated. The authors analyzed the risk factors of tumour recurrence and dropout. They treated the recurrent HCCs every time when it was possible. Their results proved the beneficial effects of the ablative therapy on the rate of dropouts (9% at 1 year), and showed that an alpha-fetoprotein (AFP) level of more than 100 ng/mL or a des-γ-carboxy prothrombin (DCP) level of more than 100 mAU/mL, and

a tumour size exceeding 3 cm (most likely due to microvascular invasion), were associated with a high probability of dropout due to tumour progression [18]. Similar results were presented in a retrospective study by Pompili et al., where 46 HCC were treated with ablative techniques (RFA and/or PEI) before transplantation, and after 9.5 months of mean waiting time the explanted livers were pathologically analyzed. The authors focused on the degree of necrosis, as a measure of the success of ablation procedure and as a factor of prolonged recurrence-free survival. Complete necrosis was found only in 43% of the treated nodules, but the rate was higher after RFA (53%). Again the best results were achieved when lesions with a diameter of less than 3 cm were ablated with RFA [19].

Our preliminary experience shows similar results to that of the larger reports. Patients with larger tumours and longer waiting times had worse results in terms of post-transplantation recurrence. The relationship between the degree of necrosis and time interval is not assessable. Because of the small number of patients and the limited availability of the thermoablative methods, it is not possible to analyze the impact of these ablative therapies on the dropout rate from the Hungarian waiting list.

We used our results combined with the results of the literature to develop a tailored future guideline for the adjuvant treatment of cirrhotic HCC patients waiting for transplantation. This guideline was based on the Barcelona Clinic Liver Cancer Group (BCLC) classification [1] and the Milan criteria [10], with additional factors, such as tumour characteristics, periodicity of the follow-up, and repeated treatments [20].

At present the guideline includes the following statements:

- For Child–Pugh Class A–B patients on the waiting list with liver cirrhosis and tumours within the Milan criteria and without portal or hepatic vein invasion: If resection is not possible, ablation should be performed as bridging therapy when the treatable nodule size is less than 3 cm, while chemoembolization or combined therapy should be carried out when the size of the tumour is 3–5 cm. Combined therapy should also be preferred when complete necrosis is not achievable with ablation(s) alone. Follow-up examinations should be adequate (multiphase contrast-enhanced imaging, tumour markers), and should be repeated every 3 months. In case of diagnosed recurrence or new HCC re-treatment should be attempted.
- For patients being evaluated for liver transplantation with HCC exceeding the Milan criteria and with a liver function precluding resection: the therapeutic methods as above should be discussed for downstaging. A successful therapy may allow the patient to enter the waiting list, but risk factors for early post-transplantation recurrence should also be assessed. In these cases,

pre-treatment histopathologic staging may help in proper selection of patients for treatment.

The uniform use of this guideline would allow to refine this approach and assess the results. Therefore the guideline has to be re-evaluated in every year and updated as ablative and embolization technology innovations and new drugs are becoming available.

Acknowledgement

Many thanks to Jane Andrew.

References

1. Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. *The Lancet* 362, 1907–1917 (2003)
2. Ishizaki Y, Kawasaki S: The evolution of liver transplantation for hepatocellular carcinoma (past, present, and future). *J Gastroenterol* 43, 18–26 (2008)
3. Lu DS, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, Durazo F, Saab S, Han S, Finn R, Hiatt JR, Busuttil RW: Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 41(5), 1130–1137 (2005)
4. Johnson EW, Holck PS, Levy AE, Yeh MM, Yeung RS: The Role of Tumor Ablation in Bridging Patients to Liver Transplantation. *Arch Surg.* 139, 825–830 (2004)
5. Galandi D, Antes G: Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma (Cochrane Review). *The Cochrane Library*, Issue 2 (2004)
6. Ebied OM, Federle MP, Carr BI, Pealer KM, Li W, Amesur N, Zajko A: Evaluation of Responses to Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma. *Cancer* 97, 1042–1050 (2003)
7. Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C: Small Hepatocellular Carcinoma in Cirrhosis: Randomized Comparison of Radio-frequency Thermal Ablation versus Percutaneous Ethanol Injection. *Radiology* 228, 235–240 (2003)
8. Nemes B, Polak W, Ther G, Hendriks H, Kóbori L, Porte RJ, Sárvári E, de Jong KP, Doros A, Gerlei Zs, van der Berg AP, Fehérvári I, Görög D, Peeters PM, Járj J, Slooff MJ: Analysis of Differences in Outcome of Two European Liver Transplant Centers. *Transplant International* 19, 372–380 (2006)
9. Bánsági Z: A rádiófrekvenciás ablatio helye a malignus daganatok kezelésében. *Lehet ségek és korlátok. Magyar Sebészet* 61(2), 59–64 (2008)
10. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334, 693–699 (1996)
11. Lubienski A: Hepatocellular carcinoma: interventional bridging to liver transplantation. *Transplantation* 80 (1 Suppl), S113–S119 (2005)
12. Poon RT, Fan ST, Lo CM, Liu CL, Wong J: Long term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 235, 373–382 (2002)
13. Belghiti J, Cortes A, Abdalla EK, Regimbeau JM, Prakash K, Durand F, Sommacale D, Dondero F, Lesurtel M, Sauvanet A, Farges O, Kianmanesh R: Resection prior to liver transplantation for hepatocellular carcinoma. *Ann Surg* 238, 885–893 (2003)
14. Maddala YK, Stadheim L, Andrews JC, Burgart LJ, Rosen CB, Kremers WK, Gores G: Drop-out rates of patients with hepatocel-

- lular cancer listed for liver transplantation: Outcome with chemoembolization. *Liver Transpl* 10; 449–455 (2004)
15. Hayashi PH, Ludkowski M, Forman LM, Osgood M, Johnson S, Kugelman M, Trotter JF, Bak T, Wachs M, Kam I, Durham J, Everson GT: Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation. *Am J Transplant* 4, 782–787 (2004)
16. Omata M, Tateishi R, Yoshida H, Shiina S: Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. *Gastroenterology* 127, S159–S166 (2004)
17. Lencioni R, Crocetti L, Petruzzi P, Vignali C, Bozzi E, della Pina C, Bargellini I, Cioni D, Oliveri F, de Simone P, Bartolozzi C, Brunetto M, Filippin F: Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: A pilot clinical study. *Journal of Hepatology* 49, 217–222 (2008)
18. Yamashiki N, Tateishi R, Yoshida H, Shiina S, Teratani T, Sato S, Mine N, Kondo Y, Kawabe T, Omata M: Ablation Therapy in Containing Extension of Hepatocellular Carcinoma: A Simulative Analysis of Dropout From the Waiting List for Liver Transplantation. *Liver Transplantation* 11, 508–514 (2005)
19. Pompili M, Mirante VG, Rondinara G, Fassati LR, Piscaglia F, Agnes S, Covino M, Ravaioli M, Fagioli S, Gasbarrini G, Rapaccini GL: Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transplantation* 11, 1117–1126 (2005)
20. Kim RD, Reed AI, Fujita S, Foley DP, Mekeel KL, Hemming AW: Consensus and Controversy in the Management of Hepatocellular Carcinoma. *J Am Coll Surg* 205, 108–123 (2007)